REMARKS

Claims 41-78 are pending in this application. Claims 41-54 and 69-78 have been withdrawn from active consideration. Claims 55-68 were the subject of examination in the outstanding Action.

Applicants traversed the restriction requirement in their response of April 21, 2008, and supplemental response of April 25, 2008. In making the restriction requirement final, the examiner asserted that the peptides disclosed in the cited Zhu et al. reference have been isolated and characterized based upon the reasons provided on page 3 of the outstanding Action. Applicants wish to state on the record that they disagree with the examiner's reasoning, as the Zhu et al. reference discloses on page 754, section 3.3, that "BmTXLP2 is an acidic protein composed of 78 residues containing 8 Cys residues which presumably form 4 disulphide bonds" (emphasis added). The reference further provides on page 750, section 2.3, that "prediction of signal sequences of precursor proteins was performed using SignallP."

Thus, the protein sequence of Bm TXLP2 was based simply on direct translation of the nucleotide sequence, and using bioinformatics Zhu et al. predicted that BmTXLP2 protein is a sodium ion channel toxin. There is no mention of the isolation

of the peptide throughout the reference and the sequence of Fig. 1(b) was obtained by mere deduction using bioinformatics based on cloned cDNA. The peptides of the reference thus have not been isolated and characterized as stated by the examiner.

The examiner has objected to claims 64-66 as being of improper dependent form on the basis that molecular weights of peptide without structural features do not provide adequate support for the scope of the claims.

As an initial point, Applicants note that claims 64 and 66 are independent, not dependent claims, and that claim 65 depends from claim 64. Applicants submit that the molecular weight of a peptide is a structural feature and, therefore, a functional limitation. Furthermore, paragraphs 0071 and 0131 of the specification identify proteins with the specified molecular weights: native JCH2 (16803 Da), JC1-P1 (16790 Da), JC2-P1 (6791 Da) and JC3-P5 (17211 Da), wherein JC1-P1, JC2-P1 and Jc3-P5 are all homologs of JCH2. Applicants submit that the molecular weights of the peptides are valid limiting structural features.

The examiner has objected to the use of the terms "variant, derivative and fragment thereof" in claims 55-57 and 66 as indefinite under 35 U.S.C. § 112, second paragraph. Applicants submit that one of ordinary skill in the art, reading the specification, in particular paragraphs 0066 - 0067, which

provide definitions of these terms, would know what is meant by these terms. Paragraph 0067 notes that "non-limiting examples of a variant, derivative or a fragment of SEQ ID No:2 are the amino acid sequences SEQ ID NOs:3 to 13." Thus, adequate support is provided for the terms "variant," "derivative" and "fragment" in the specification and as such the claims point out the subject matter which Applicants regard as the invention. Furthermore, claims 55 and 56 focus on peptides comprising the amino acid sequences of SEQ ID Nos: 3-13 and so are set forth with great particularity and definiteness.

The examiner further has rejected claims 55-59 and 61-67 under 35 U.S.C. § 112 on the basis that they fail to comply with the written description requirement. The examiner asserts that claims 55-58 and 66 recite that the peptide comprises SEQ ID NO:2 or a variant, derivative or a fragment thereof and that, as such, innumerable polypeptides of unknown sequences are being claimed. Without conceding to the examiner's assertions, but for the purpose of advancing the prosecution of this application, claims 55 and 66 have been amended above to change "comprises" to "consisting of."

Applicants respectfully submit that one of skill in the art reading the amended claims together with the specification, in particular page 18, will know immediately what is meant by the

phrase "variant, derivative and/or fragment thereof of SEQ ID No:2" having the enumerated activities. Applicants further note that claims 56 and 57 specify the amino acid sequences of the fragments claimed; the subject matter of these claims is set forth with great particularity.

The examiner asserted that providing the molecular weights of peptides as representative species as in claim 64 does not provide adequate written description support to the claims. Applicants point out that paragraphs 007 and 0131 of the specification as originally filed disclose the very proteins which have the molecular weights recited in claim 64 and that there thus is adequate written description support in the specification.

The examiner noted that the molecular weight claimed for each of the specific homologs of the present invention represents a molecular weight about 40% higher as compared to the molecular weight of the peptide of SEQ ID NO:2. Applicants note that as mentioned in paragraphs 0048 and 0131, mass spectrophotometer analysis revealed that the mass of purified native JCH2 was found to be 16803 Da, as shown in figure 4. As mentioned in paragraph 0131, "Interestingly, the mass of 16 kDa (obtained from protein analysis) does not correlate to the mass deduced from cDNA. The mass deduced from the cDNA sequence is 8132 Da, while the mass of

native protein was determined to be 16803 Da."

Furthermore, as mentioned in paragraphs 0069 and 0071, homologs can be obtained from venom of any known species and examples are provided of homologs obtained from the same venom of *Buthus martensii* Karsch and showing inhibition on HMGCoA reductase activity, inhibition of phosphomevalonate, reduction in the accumulation of cholesterol in the cholesterol biosynthesis pathway and/or reduction in the level of serum cholesterol, including 16790 DA (JC1-P1); 16791Da (JC2-P1) and 17211Da (JC3-P5). These homologs have similar molecular weights as native JCH2. There thus is no discrepancy between the actual molecular weight of SEQ ID NO:2 and the molecular weight claimed for the peptides.

Claims 55-59 have been rejected under 35 U.S.C. §102(b) as anticipated by Possani et al. The examiner asserted that the claims are directed to an isolated peptide comprising the amino acid sequence of SEQ ID NO:2 or a variant, derivative or fragment thereof having the function of reducing the level of cholesterol. The cited reference was said to disclose peptide toxin PiL, which comprises the tripeptide sequence -CQQ- between the amino acid residues 40 and 50 that correspond to amino acids 37-39, a fragment of the elected species SEQ ID NO:3. The examiner asserted that as the reference discloses a peptide fragment that

corresponds to the instant peptide SEQ ID NO:3, it is inherent the peptide exhibits the function of reducing serum cholesterol. He further asserted that the reference discloses that the peptide is isolated from scorpion venom and so reads on claims 58 and 59. This rejection is traversed.

The examiner has asserted that the reference discloses a peptide fragment that "corresponds" to the peptide of SEQ ID NO:3 and that it therefore is "inherent" that the peptide exhibits the function of reducing serum cholesterol. The reference does not disclose an isolated three amino acid peptide having the sequence of a three amino acid fragment of SEQ ID NO:3. The three amino acid sequence noted by the examiner is only described as part of a longer sequence, and there is nothing in the reference to suggest isolating that particular 3 amino acid portion. Neither that longer sequence nor the 3 amino acid sub-sequence of the reference corresponds to the sequence of SEQ ID NO:3, which is a 72 amino acid fragment of the peptide of SEQ ID NO:2. Furthermore, the examiner has asserted that it is "inherent" that the 3 amino acid peptide of the reference will have the activity of the peptides of the claims, but there is nothing in the reference to indicate that this is true. There is no basis in the record for the examiner's conclusion. The Possani reference focuses on peptides that affect sodium, potassium, calcium and

chloride ion channels; there is no teaching or suggestion that any of the disclosed fragments--or portions of those fragments--have the function of reducing serum cholesterol levels. As a final point, Applicants note that claims 56 and 57 require that the peptide claimed comprises the amino acid sequence of any of SEQ ID NOS: 3-13, none of which corresponds to the PiL sequence or the three amino acid sub-fragment highlighted by the examiner. The cited reference thus does not anticipate claims 55-59 of the present application.

Claims 55-60 and 63 have been rejected under 35 U.S.C. § 102(b) as anticipated by the Zhu et al. publication. The examiner asserted that the reference discloses the elected species of SEQ ID NO:3. The reference was said to disclose the peptide from a cDNA library prepared from venom glands of *Buthus martensii* Karsch scorpions using molecular cloning techniques. This rejection is traversed.

The authors of the reference had only the nucleotide sequence encoding the peptide and deduced the amino acid sequence from that. In contrast, the claims at issue are directed to an isolated peptide or fragments or variants thereof. As the authors did not have an isolated peptide, the reference does not anticipate the claims. The isolated peptide has a secondary structure different from that predicted by Zhu et al. and an

activity different from that suggested by Zhu et al. based upon their predicted structure.

Furthermore, as the reference does not disclose an isolated peptide, it certainly does not disclose specific fragments of the peptide (SEQ ID Nos: 3-13) such as set forth in claim 56, or fusion peptides containing the peptide or specific fragments thereof as in claim 57.

Claims 61 and 66-68 have been rejected under 35 U.S.C. § 103(a) as unpatentable over the Zhu et al. reference relied upon above in view of Torres-Larios, *Eur. J. Biochem.* 267:5023-5031 (2000). The examiner asserted that the primary reference discloses the source and the peptide sequences of the present invention and that the secondary reference teaches how a peptide can be isolated and purified from scorpion venom for pharmaceutical purposes. He further asserted that there would have been a reasonable expectation of success in combining the references as Torres-Larios successfully purified the peptide from venom from *Hadrurus aztecus* and the techniques could be applied to the peptide from *Buthus martensii* Karsch. This rejection is traversed.

Applicants submit that combining the teachings of the two references would not result in obtaining the isolated peptide of claim 55. Claim 61 has been amended to include that following

gel filtration, at least one fraction is selected that has HMGCoA reductase inhibition and then reverse phase HPLC is performed on that fraction. The peptide of the present application has the function of HMGCoA reductase inhibitor, reducing the accumulation of cholesterol in the cholesterol biosynthesis pathway and/or reducing the level of serum cholesterol.

In contrast, Zhu et al. suggest that the peptide of Figure 1(b) is a sodium ion channel toxin. They taught in Section 3.3 of their paper that what they called the BmTXLP2 protein has 78 amino acid residues containing 8 Cys residues forming 4 disulphide bonds, a deduction based simply on direct translation of the nucleotide sequence, and they used bioinformatics to predict that the protein is a sodium ion channel toxin.

Torres-Larios focused on a method of isolating from the venom of scorpion *Hadrurus aztecus* a peptide having antimicrobial and cytolytic activity. As the present invention relates to isolated peptides consisting of SEQ ID NO:2 or variants, derivatives and/or fragments thereof, and, in particular, a peptide that may be purified from *Buthus martensii* Karsch, one of skill in the art would not have been motivated to refer to the teachings of Torres-Larios. Furthermore, if a skilled person did refer to Torres-Larios, combining the teachings of that reference with those of the Zhu et al. paper would not have resulted in the

production of the peptide of SEQ ID NO:2 or fragments or variants thereof as nothing in the two references discusses or suggests obtaining a peptide having HMGCoA reductase activity.

In view of the forgoing amendments and discussion, Applicants respectfully submit that the claims are in condition for allowance.

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